

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 12 June 2001 (12.06.01)	
<b>International application No.</b> PCT/US00/24746	<b>Applicant's or agent's file reference</b> X13527PCT
<b>International filing date</b> (day/month/year) 11 September 2000 (11.09.00)	<b>Priority date</b> (day/month/year) 20 September 1999 (20.09.99)
<b>Applicant</b> HOCK, Janet, M.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

07 March 2001 (07.03.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b> Cécile Chatel (Fax 338.87.40)
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WEBSTER, Thomas D.  
ELI LILLY AND COMPANY  
Lilly Corporate Center  
Indianapolis, Indiana 46285  
ETATS-UNIS D'AMERIQUE

RECEIVED

JAN 09 2002

ELI LILLY & COMPANY  
PATENT DIVISION

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing (day/month/year)	13.12.2001
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Applicant's or agent's file reference X-13527	IMPORTANT NOTIFICATION
--------------------------------------------------	------------------------

International application No. PCT/US00/24746	International filing date (day/month/year) 11/09/2000	Priority date (day/month/year) 20/09/1999
-------------------------------------------------	----------------------------------------------------------	----------------------------------------------

Applicant  
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
---------------------------------------	--------------------



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REC'D 17 DEC 2001

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)


Applicant's or agent's file reference X-13527	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/24746	International filing date (day/month/year) 11/09/2000	Priority date (day/month/year) 20/09/1999	
International Patent Classification (IPC) or national classification and IPC A61K38/29			
Applicant ELI LILLY AND COMPANY et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
  - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  07/03/2001	Date of completion of this report  13.12.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Deck, A  Telephone No. +49 89 2399 8432





I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-23 as originally filed

**Claims, No.:**

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):





(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-19.

because:

- ☒ the said international application, or the said claims Nos. 1-19 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	2-13, 16, 18, 19
	No:	Claims	1, 14, 15, 17, 20-23
Inventive step (IS)	Yes:	Claims	2-13, 16, 18, 19
	No:	Claims	1, 14, 15, 17, 20-23
Industrial applicability (IA)	Yes:	Claims	20-23



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/24746

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No: Claims see separate sheet

2. Citations and explanations  
**see separate sheet**



**Section III:**

Claims 1-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Section V:**

1. The following document is referred to:

D1: US-A-5 840 690 (HOLICK MICHAEL F) 24 November 1998 (1998-11-24)

2. The document D1 discloses the use of human PTH or fragments thereof (e.g. PTH(1-34)) in the treatment of cancer (see column 4, lines 9-14; column 12, lines 12-20).

The present invention is directed to the reduction of the risk of developing cancer, but the treatment of already declared cancer seems to be encompassed as well as can be understood from claim 19 and from the description page 7, lines 14-15 and page 8, lines 16-21. Therefore, as the claimed subject-matter is not strictly restricted to the reduction of the risk of developing *undeclared* cancer, claims 1, 14, 15, 17 and 23 are not new in view of D1.

The subject-matter of claims 20-22 is not new either as the process of manufacturing a medicament with PTH as the active ingredient is not new in view of D1. The indication of the intended use is not limiting as PTH is already described in pharmaceutical formulation.

3. In the case the novelty objection would be overcome, the invention could possibly be inventive as none of the prior art disclose the reduction of the *risk of developing* cancer.
4. For the assessment of the present claims 1-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The



patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.





## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>3797.41WOU1</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 24746</b>	International filing date (day/month/year) <b>11/09/2000</b>	(Earliest) Priority Date (day/month/year) <b>20/09/1999</b>
Applicant <b>ELI LILLY AND COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

==  
☐ None of the figures.



## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/29 A61P35/04 A61P19/08 //(A61K38/29,31:59),  
(A61K38/29,30:06),(A61K38/29,31:59,30:06)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH, CANCERLIT

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 840 690 A (HOLICK MICHAEL F) 24 November 1998 (1998-11-24) column 3, line 64 -column 4, line 14 claims 1-11 ---	1,14,15, 17,20-23
A	EP 0 878 201 A (CHUGAI PHARMACEUTICAL CO LTD) 18 November 1998 (1998-11-18) the whole document ---	1-23
A	WO 96 03437 A (SANDOZ AG ;GAMSE RAINER (CH); SANDOZ LTD (CH); CARDINAUX FRANCOIS) 8 February 1996 (1996-02-08) page 15, line 30 -page 16, line 2 ---	1-23
A	EP 0 197 514 A (GEN HOSPITAL CORP) 15 October 1986 (1986-10-15) the whole document --- -/--	1-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

20 February 2001

Date of mailing of the international search report

01/03/2001

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Stein, A



## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TREMBLING P ET AL: "Comparison of effects of PTHrP 1-34, PTHrP 1-86 and PTH on proliferation of breast cancer cells." JOURNAL OF ENDOCRINOLOGY, vol. 144, no. SUPPL., 1995, page P223 XP000982364 ISSN: 0022-0795 the whole document ----	1-23
A	DELMAS P D ET AL: "Bone loss induced by cancer treatment and its management." EUROPEAN JOURNAL OF CANCER, vol. 34, no. 2, February 1998 (1998-02), pages 260-262, XP000982362 ISSN: 0959-8049 the whole document ----	10,13,19
A	AIGINGER P ET AL: "THERAPY OF MULTIPLE BONE METASTASES WITH PARATHYROID HORMONE AND RADIO PHOSPHORUS" OESTERREICHISCHE ZEITSCHRIFT FUER ONKOLOGIE, vol. 2, no. 1, 1975, pages 17-24, XP000982314 ISSN: 0377-2004 the whole document -----	1,16-23



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P 00/24746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5840690 A	24-11-1998	US 5527772 A	18-06-1996
		US 6066618 A	23-05-2000
		WO 9204039 A	19-03-1992
		AT 138685 T	15-06-1996
		AU 2788089 A	23-05-1989
		CA 1326460 A	25-01-1994
		DE 3855331 D	04-07-1996
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		EP 0415924 A	13-03-1991
		JP 2802084 B	21-09-1998
		JP 3505517 T	05-12-1991
		WO 8903873 A	05-05-1989
EP 0878201 A	18-11-1998	AU 1558197 A	22-08-1997
		JP 9301887 A	25-11-1997
		WO 9727870 A	07-08-1997
WO 9603437 A	08-02-1996	AU 3167095 A	22-02-1996
		BR 9508433 A	14-07-1998
		CA 2192787 A	08-02-1996
		CZ 9700233 A	16-07-1997
		EP 0773958 A	21-05-1997
		FI 970168 A	15-01-1997
		HU 77979 A	28-01-1999
		JP 10502091 T	24-02-1998
		NO 970356 A	28-01-1997
		PL 318017 A	12-05-1997
		SK 12097 A	06-08-1997
		TR 960095 A	21-06-1996
		ZA 9506331 A	28-01-1997
EP 0197514 A	15-10-1986	AT 79271 T	15-08-1992
		AU 599905 B	02-08-1990
		AU 5561686 A	09-10-1986
		CA 1288695 A	10-09-1991
		DE 3686343 A	17-09-1992
		DE 3686343 T	28-01-1993
		DK 155686 A	05-10-1986
		IE 59620 B	09-03-1994
		IL 78342 A	10-06-1991
		JP 7072138 B	02-08-1995
		JP 62000033 A	06-01-1987
		JP 2531505 B	04-09-1996
		JP 7179358 A	18-07-1995
		PH 23720 A	03-11-1989
		US 4698328 A	06-10-1987
		ZA 8602510 A	26-11-1986







## INTERNATIONAL APPLICATION PUBLISHED

(51) International Patent Classification n<sup>6</sup> :

C07K 14/635, A61K 38/29

A1

WO 9603437A1

(43) International Publication Date: 8 February 1996 (08.02.96)

(21) International Application Number: PCT/EP95/02993

(22) International Filing Date: 27 July 1995 (27.07.95)

## (30) Priority Data:

9415254.3	28 July 1994 (28.07.94)	GB
9415255.0	28 July 1994 (28.07.94)	GB

(71) Applicant (for all designated States except AT DE US): SANDOZ LTD. [CH/CH]; Lichtstrasse 35, CH-4002 Basle (CH).

(71) Applicant (for DE only): SANDOZ-PATENT-GMBH [DE/DE]; Humboldtstrasse 3, D-79539 Lörrach (DE).

(71) Applicant (for AT only): SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

## (72) Inventors; and

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(74) Common Representative: SANDOZ LTD.; Patents &amp; Trade-mark Div., Lichtstrasse 35, CH-4002 Basle (CH).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

## Published

*With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: PTH OR PTHrP ANTAGONISTS

## (57) Abstract

PTH or PTHrP compounds having potent antagonistic activity at the PTH/PTHrP receptor in which at least one of the amino acid residues naturally occurring in positions 2 and 10 is replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain, and optionally at least one of the amino acid residues naturally occurring in positions 3 and 6 is further replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain, having pharmacological activity, e.g. prevention or treatment of conditions which are associated with increased plasma calcium caused by excessive release of PTH or PTHrP.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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FR	France			VN	Viet Nam
GA	Gabon				

## PTH or PTHrP antagonists

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The present invention relates to parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) compounds, a process for their production, pharmaceutical preparations comprising them and their use as a pharmaceutical.

- 10 More particularly the present invention provides a PTH or PTHrP compound having potent antagonistic activity at the PTH/PTHrP receptor in which at least one of the amino acid residues naturally occurring in positions 2 and 10 is replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic
- 15 group on its side chain, and optionally at least one of the amino acid residues naturally occurring in positions 3 and 6 is further replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain. The compounds are hereinafter referred to as compounds of the invention.
- 20 In a particular embodiment of the invention there is provided a PTH or PTHrP compound in which the amino acid residue naturally occurring in position 10 is replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain, and optionally at least one of the amino acid
- 25 residues naturally occurring in positions 3 and 6 is further replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain.

- The term "PTHrP" refers to any naturally occurring form of PTHrP, e.g. human, bovine, chicken, rat or mouse PTHrP. For consistency
- 30 and as is conventional, in the following description, the same numbering system will be applied to the amino acid residues of the PTHrP sequence regardless of whether any  $\alpha$ -amino acid residue of the PTHrP sequence is replaced or omitted according to the invention.

- 35 The term "PTH" refers to any naturally occurring form of PTH, e.g. human, bovine, chicken, rat or mouse PTH. For consistency and as is conventional, in the following description, the same numbering system will be applied to the amino acid residues of the PTH

sequence regardless of whether any  $\alpha$ -amino acid residue of the PTH sequence is replaced or omitted according to the invention.

By "PTHrP compound" or "PTH compound" is meant a peptide comprising an amino acid sequence based on a N-terminal fragment of PTHrP or  
5 PTH respectively, preferably based on a PTHrP or PTH fragment starting with any one of the residues 1-7 and terminating with any one of the residues from 27 to 38 e.g. a N-terminal fragment of PTHrP or PTH comprising up to 31, 34, 35, 36, 37 or 38 amino acid residues. The terms "PTHrP or PTH" will thus be understood as  
10 embracing peptides wherein one or more amino acid residues of the said N-terminal fragment is omitted, preferably at the N-terminus. The terms are also to be understood as embracing peptides wherein one or more amino acid residues of the naturally occurring sequence is replaced by one or more other amino acid residues (natural or  
15 non natural) in addition to the substitution in position 2 and/or 10 and optionally in 3 and/or 6 according to the invention. The 1-38, 1-34 and 1-31 N-terminal fragments of human PTHrP have the sequences as indicated in SEQ ID No:1, 2 or 3, respectively.

The 1-38, 1-34 and 1-31 N-terminal fragments of human PTH have the  
20 sequences as indicated in SEQ ID No:4, 5 or 6, respectively.

The N-terminus of the PTHrP or PTH compounds may be a free or a protected amino group, bearing e.g. a N-protecting group as disclosed in "Protective Groups in Organic Synthesis", T.W. Greene, J. Wiley & Sons NY (1981), 219-287, the contents of which being  
25 herein incorporated by reference, preferably protected by R"-CO-, R"-O-CO-, R"-O-CH<sub>2</sub>-CO- or R"-SO<sub>2</sub>, or an amino group bearing a radical R''', R'''-NH-CO- or R'''-NH-CS- such as defined hereunder.

The C-terminus of the compounds of the invention may be COOH, CONH<sub>2</sub>, or a mono- or disubstituted amide, e.g. -CONR<sub>c</sub>R<sub>d</sub> wherein one of R<sub>c</sub>  
30 and R<sub>d</sub> is H and the other is an aliphatic residue, e.g. C<sub>1-6</sub>alkyl, or both are an aliphatic residue, or R<sub>c</sub> and R<sub>d</sub> together with the nitrogen atom to which they are attached form a heterocyclic residue, e.g. pyrrolidinyl or piperidinyl.

PTHrP or PTH compounds in accordance with the invention have potent  
35 antagonistic activity at the PTH/PTHrP receptor e.g. bind to the PTH/PTHrP receptor, have an intrinsic activity (i.a) for activation of the PTH/PTHrP receptor in a functional bioassay significantly <1, e.g. an i.a of at most 0.3, and antagonize PTHrP or PTH or a

fragment thereof e.g. PTHrP(1-34) or PTH(1-34) in a functional bioassay with a pA2 value of at least 6.5. Preferably compounds in accordance with the invention have an i.a of 0.03 or lower or even not detectable in some of the assays. Example of a functional  
 5 bioassay is the osteosarcoma-based adenylate cyclase assay employed conventionally in the art. This assay provides an in vitro determination of the extent to which the compound to be tested stimulates adenylate cyclase activity or antagonizes the effect of PTHrP or PTH or a fragment thereof in rat osteosarcoma cells of the  
 10 UMR lineage, e.g. UMR-106-06 according to the method of Marcus and Aurbach in Endocrinology, 85, 801-810 (1969) as disclosed hereinafter.

By amino acid is meant a naturally occurring or commercially available or non natural amino acid or an optical isomer thereof.  
 15 A non natural amino acid is an amino acid which is not incorporated into a protein under mRNA direction, e.g.  $\beta$ -Nal, a fluoro- $\alpha$ -amino acid such as fluoroalanine, cyclohexylalanine or trimethylsilyl-alanine.

"Natural amino acids" refer to those well known in the art. They  
 20 are listed and standard abbreviations are provided in the U.S.P.T.O. publication, Trademark Official Gazette, published May 15, 1990, p. 33 at 46. These amino acids and abbreviations are specifically incorporated herein by reference.

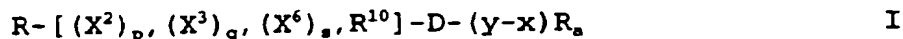
The natural amino acids are shown below:

25	A	Ala	alanine
	D	Asp	aspartic acid
	E	Glu	glutamic acid
	F	Phe	phenylalanine
	G	Gly	glycine
30	H	His	histidine
	I	Ile	isoleucine
	K	Lys	lysine
	L	Leu	leucine
	M	Met	methionine
35	N	Asn	asparagine
	Q	Gln	glutamine
	R	Arg	arginine
	S	Ser	serine
	T	Thr	threonine
40	V	Val	valine

W	Trp	tryptophane
Y	Tyr	tyrosine

By amino acid residue bearing an aromatic or heteroaromatic group on its side chain is meant an amino acid residue wherein the side chain is e.g. optionally ring-substituted phenyl-methyl, 1- or 2-naphthyl-methyl, 1- or 2-naphthyl-ethyl, 3- or 4-pyridyl-methyl, 3-indolyl-methyl or 3-indazolyl-methyl; preferably it is an amino acid residue of formula  $\text{-NH-CHR'-CO-}$  as defined below.

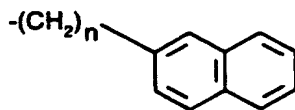
According to a preferred embodiment of the invention, there is provided a compound of formula I



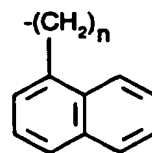
wherein

- x is a residue number selected from 31, 34, 35, 36, 37 or 38,  
 y is a residue number selected from 1, 2, 3, 4, 5, 6 or 7,  
 15  $\text{X}^2$  is Val or has independently one of the significances of  $\text{X}^{10}$ ,  
 $\text{X}^3$  is Ser or has independently one of the significances of  $\text{X}^{10}$ ,  
 $\text{X}^6$  is Gln or has independently one of the significances of  $\text{X}^{10}$ ,  
 $\text{R}^{10}$  is Asp or  $\text{X}^{10}$ ,  $\text{X}^{10}$  being Trp or  $\text{-NH-CHR'-CO-}$  wherein R' is a radical of formula (a), (b), (c) or (d)

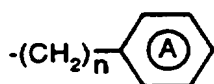
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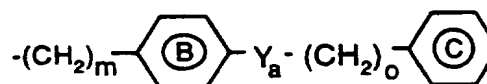
(a)



(b)



(c)



(d)

wherein

n is 1 or 2,

m is 1 or 2,

o is 0 or 1,

25 ring A is optionally substituted by one or more substituents

- selected from fluoro, chloro, nitro, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy, whereby two alkyl or two alkoxy substituents may also form together a ring structure fused to ring A, each of rings B and C independently may be substituted as indicated above for ring A, and
- 5 Y<sub>a</sub> is a direct bond, -CH<sub>2</sub>-, O, NH or N-C<sub>1-6</sub>alkyl,
- D is an amino acid sequence derived from an N-terminal fragment of PTHrP or PTH,
- each of p, q and s is 1, provided that p is 0 when y > 2,
- 10 q is 0 when y > 3 and s is 0 when y > 6,
- R is H, R"-CO-, R"-O-CO-, R"-O-CH<sub>2</sub>-CO-, R"-SO<sub>2</sub>-, R''', R'''-NH-CO-, R'''-NH-CS- or NH<sub>2</sub>-C<sub>1-6</sub>alkylene-CO- wherein R" is C<sub>1-8</sub>alkyl; ω-carboxy-C<sub>1-6</sub>alkyl; ω-[(C<sub>1-4</sub>alkoxy)-carbonyl]-C<sub>1-6</sub>alkyl; C<sub>2-8</sub>alkenyl; C<sub>5-7</sub>cycloalkyl; C<sub>5-7</sub>cycloalkyl-C<sub>1-4</sub>alkyl; or phenyl, phenyl-C<sub>1-4</sub>alkyl, 1-naphthyl, 2-naphthyl, 15 1-naphthyl-C<sub>1-2</sub>alkyl or 2-naphthyl-C<sub>1-2</sub>alkyl each of which being optionally ring substituted by one or more substituents selected from fluoro, chloro, nitro, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy; heteroaryl; and
- 20 R''' has independently one of the significances given for R" except the significances of ω-carboxy-C<sub>1-6</sub>alkyl and ω-[(C<sub>1-4</sub>alkoxy)-carbonyl]-C<sub>1-6</sub>alkyl; and
- R<sub>a</sub> is OH or NH<sub>2</sub>,
- with the proviso that at least one of X<sup>2</sup> and R<sup>10</sup> has the
- 25 significance of X<sup>10</sup>.

When the substituents of ring A, B or C form together a ring structure, it may be e.g. -O-CH<sub>2</sub>-CH<sub>2</sub>-O-. Example of polycyclic cycloalkyl is e.g. adamantyl.

- By heteroaryl as R" is meant a 5-, 6- or 7-membered unsaturated
- 30 heterocyclic radical comprising at least one nitrogen atom and optionally further a heteroatom such as N, O or S, and optionally condensed with a benzene ring. Heteroaryl is preferably indolyl, quinolyl or isoquinolyl.

- The compounds of the invention may exist e.g. in free form, salt
- 35 form or in the form of complexes thereof. Acid addition salts may be formed with e.g. organic acids, polymeric acids and inorganic acids. Such acid addition salt forms include e.g. the hydrochlorides and the acetates. Complexes are e.g. formed from the PTHrP or PTH compound of the invention on addition of inorganic

substances, e.g. inorganic salts or hydroxides such as Ca- and Zn-salts, and/or an addition of polymeric organic substances.

In the compounds of formula I, the following significances are preferred either individually or in any combination or

5 sub-combination:

1. D is an N-terminal fragment of hPTHrP.
2. D is an N-terminal fragment of hPTH.
3.  $X^{10}$  is Trp.
- 10 4.  $X^{10}$  is  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c), preferably (a) or (c), more preferably (a).
5.  $X^2$  is Trp or  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c),
6. Each of  $X^2$  and  $X^{10}$  is Trp or  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c).
- 15 7. Each of  $X^3$  and  $X^{10}$  is Trp or  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c).
8. Each of  $X^6$  and  $X^{10}$  is Trp or  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c).
- 20 9. Each of  $X^2$ ,  $X^6$  and  $X^{10}$  is Trp or  $-NH-CHR'-CO-$  wherein  $R'$  is a radical of formula (a), (b) or (c).
10. n is 1.
11. y is a residue number selected from 3, 4, 5, 6 or 7, preferably 3 or 5.
12. x is a residue number selected from 31 or 34.
- 25 13. R is  $R''CO-$ ,  $R''-SO_2$ ,  $R'''$  or  $H_2N-C_{1-6}alkylene-CO-$ .
14.  $R''$  is  $C_{1-8}alkyl$ , phenyl $C_{1-4}alkyl$ , 1- or 2-naphthyl, 1- or 2-naphthyl- $C_{1-2}alkyl$ .



15. R is  $\omega$ -carboxy-C<sub>1-6</sub>alkyl.

As already mentioned, one or more amino acid residues at positions other than 2 and/or 10 may be further replaced by a natural or unnatural amino acid residue as indicated above or be omitted.

5 When the compounds of the invention are hPTHrP derivatives, they may comprise further amino acid replacement, e.g. in position 3, e.g. Ala, in position 4, e.g. Trp, in position 5, e.g. optionally ring-substituted Phe, in position 11 and/or 13, e.g. Leu, or in position 34, e.g. D-Ala; their amino acid sequence being optionally  
10 shortened at the N-terminus by the omission of 1 up to 7 amino acid residues. When the compounds of the invention are hPTH derivatives, amino acid residues may be further replaced e.g. in at least one of the positions selected from 8, 16, 18, 33 and 34, e.g. Leu<sup>8</sup>, Ala<sup>16</sup>, Gln<sup>18</sup>, Thr<sup>33</sup>, Ala<sup>34</sup> or D-isomers thereof.

15 The present invention also provides a process for the production of the PTHrP or PTH compounds of the invention. They may be prepared in a stepwise manner either in solution or using the solid phase synthesis process or genetic engineering or by a combination of these methods.

20 The compounds of the invention may be produced for example as follows by:

- a) removing at least one protecting group which is present in a PTHrP or PTH compound of the invention, e.g. a compound of formula I, in protected form; or
- 25 b) linking together by an amide bond two peptide fragments in protected, partially protected or unprotected form, the peptide fragments being such that the amino acid sequence of the desired PTHrP or PTH compound, e.g. of formula I, is obtained, and then effecting optionally stage a) of the process, or
- 30 c) adding a protecting group or substituent in a selective manner to the amino group of the N-terminal residue of the desired sequence or N-terminal fragment thereof in protected or unprotected form and then optionally carrying out step a),

and recovering the PTHrP or PTH compounds thus obtained in free form, in salt form or in complex form.

Process steps a), b) and c) may be effected in analogy with known methods, e.g. as known in the art of peptide chemistry or as  
5 described in the following examples. Where desired, in these reactions, protecting groups which are suitable for use in peptides may be used for functional groups which do not participate in the reaction. The term protecting group may also include a polymer resin having functional groups.

10 When the compounds of the invention comprise unnatural and natural residues, they may be produced by a combination of a chemical stepwise process and genetic engineering; the peptide sequence (whether the complete sequence or a fragment) made of genetically encodable amino acid residues may be produced by recombinant  
15 techniques and the desired unnatural amino acids or terminal amino substituent may be introduced by chemical synthesis and, where required, the fragments may be combined and the protecting group(s) when present may be removed.

In the following Examples all temperatures are in °C. The following  
20 abbreviations are employed.

DMF	=	dimethylformamide
DMA	=	N,N-dimethylacetamide-6-sulfonyl
Pmc	=	2,2,5,7,8-pentamethylchroman
tBu	=	tert.butyl
25 PyBOP	=	Benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
Nal(2)	=	L-3-(2-naphthyl)-alanine
DIEA	=	N,N-diisopropyl-N-ethylamine
Fmoc	=	9-fluorenylmethoxycarbonyl
30 RT	=	room temperature
MS	=	M <sup>+</sup> determined by electrospray spectroscopy

**EXAMPLE 1:** [Trp<sup>4,10</sup>]hPTHrP(1-34) OH

The peptide is synthesized in a stepwise manner on a polystyrene based resin support. The alpha-amino group is protected by Fmoc  
35 and the side-chain functional groups are protected as follows: Asp(OtBu), Glu(OtBu), His(Trt), Lys(Boc), Asn(Trt), Gln(Trt),

Arg(Pmc), Ser(tBu), Trp(Boc) and Thr(tBu).

Fmoc-Ala-oxymethyl-4-phenoxy-methyl-co(polystyrene-1%-divinyl-benzene), approx. 0.5 mmol/g, is used as a starting material for the stepwise solid phase synthesis of peptides which consists of  
5 repetitive cycles of alpha-amino group deprotection, washing, coupling (i.e., attachment of next amino acid residue to the growing peptide chain) and washing. The N-alpha Fmoc group is cleaved using piperidine, 20% in DMA. In the coupling reaction four equivalents of Fmoc-amino acid and PyBOP-reagent and eight  
10 equivalents of DIEA in DMA are used per amino-group. After complete assembly of the peptide chain the terminal Fmoc-protecting group is removed with piperidine in DMA as before. The peptide is cleaved from the resin support and all side-chain protecting groups are simultaneously removed by using a reagent  
15 consisting of 5% of dodecylmethylsulfide and 5% water in TFA for two hours at RT. Resin particles are filtered off, washed with some TFA and the product is precipitated from the combined filtrates by the addition of 10 to 20 volumes of diethyl ether, washed with ether and dried. The product is purified by  
20 chromatography on a C-18 wide-pore silica column using a gradient of acetonitrile in 2% aqueous phosphoric acid. Fractions containing the pure compound are collected, filtered through an anion-exchange resin (Biorad, AG4-X4 acetate form) and lyophilized to give the title compound.

25 MS: 4146

In analogy with the procedure of Example 1, but using the appropriate amino-acids the following compounds may be prepared:

<b>EXAMPLE 2:</b>	[Trp <sup>10</sup> , Leu <sup>11</sup> , Leu <sup>13</sup> ]hPTHrP(1-34)OH	MS: 4059
<b>EXAMPLE 3:</b>	[Trp <sup>10</sup> , Leu <sup>11</sup> ]hPTHrP(1-34)OH	MS: 4073
30 <b>EXAMPLE 4:</b>	[Trp <sup>3,10</sup> ]hPTHrP(1-34)OH	MS: 4188
<b>EXAMPLE 5:</b>	[Trp <sup>2,10</sup> ]hPTHrP(1-34)OH	MS: 4176
<b>EXAMPLE 6:</b>	[Trp <sup>10</sup> ]hPTHrP(2-34)OH	MS: 4018.3
<b>EXAMPLE 7:</b>	[Trp <sup>10</sup> ]hPTHrP(3-34)OH	MS: 3919.2
<b>EXAMPLE 8:</b>	[Trp <sup>2</sup> ]hPTHrP(1-34)OH	MS: 4104.9
35 <b>EXAMPLE 9:</b>	[Trp <sup>10</sup> ]hPTH(1-34)OH	MS: 4189

**EXAMPLE 10:** [Leu<sup>8</sup>, Trp<sup>10</sup>, Ala<sup>16</sup>, Gln<sup>18</sup>, Thr<sup>33</sup>, Ala<sup>34</sup>]hPTH(1-34)OH  
MS: 4036

**EXAMPLE 11:** [Leu<sup>8</sup>, Trp<sup>10</sup>, Ala<sup>16</sup>, Gln<sup>18</sup>, Thr<sup>33</sup>, Ala<sup>34</sup>]hPTH(2-34)OH

MS: 3949

**EXAMPLE 12:** [Leu<sup>8</sup>, Trp<sup>10</sup>, DLeu<sup>11</sup>, Gln<sup>18</sup>, Thr<sup>33</sup>, Ala<sup>34</sup>]hPTH(1-34)OH

MS: 4079

5 **EXAMPLE 13:** [Phe<sup>2</sup>, Trp<sup>10</sup>]hPTHrP(1-34)-OH MS: 4137.1

**EXAMPLE 14:** [Trp<sup>2</sup>, Trp<sup>10</sup>]hPTHrP(2-34)-OH MS: 4105.1

**EXAMPLE 15:** [Trp<sup>6</sup>, Trp<sup>10</sup>]hPTHrP(1-34)-OH MS: 4146.8

**EXAMPLE 16:** [Trp<sup>6</sup>, Trp<sup>10</sup>]hPTHrP(6-34)-OH MS: 3623.3

**EXAMPLE 17:** [Trp<sup>10</sup>]hPTHrP(7-34)-OH MS: 3437.6

10 **EXAMPLE 18:** [Trp<sup>3</sup>, Trp<sup>10</sup>]hPTHrP(3-34)-OH MS: 4018.0

**EXAMPLE 19:** [Trp<sup>10</sup>]hPTHrP(1-34)OH MS: 4088.7

**EXAMPLE 20:** [Trp<sup>6</sup>, Trp<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub> MS: 3976.8

**EXAMPLE 21:** [Phe<sup>6</sup>, Trp<sup>10</sup>]hPTHrP(1-34)OH MS: 3546.1

**EXAMPLE 22:** [Phe<sup>2</sup>, Phe<sup>6</sup>, Trp<sup>10</sup>]hPTHrP(1-34)OH MS: 4155.1

15 **EXAMPLE 23:** N<sup>ε</sup>-3-aminopropionyl-[Phe<sup>6</sup>, Nal(2)<sup>10</sup>]hPTHrP(4-34)NH<sub>2</sub>

MS: 3932.0

**EXAMPLE 24:** N<sup>ε</sup>-benzyloxycarbonyl[Nal(2)<sup>10</sup>]hPTHrP(3-34)-NH<sub>2</sub>

This peptide is prepared in a manner analogous to Example 1 but using 4-(2',4'-dimethoxyphenyl-Fmoc-amino-methyl)-phenoxy-

20 co(polystyrene-1%-divinylbenzene), approx. 0.4 mmol/g, which may be prepared, e.g., as described in Tetrah. Letters, 28:3787-3790 (1987) as a starting material. In the last synthesis cycle Z-Ser-OH is added to the peptide chain and the peptide cleaved and purified as in Example 1.

25 MS: 3975.3

**EXAMPLE 25:** N<sup>ε</sup>-acetyl-[Trp<sup>10</sup>]hPTHrP(3-34)OH

This peptide is assembled in analogy with the procedure of Example 1. At the end of the synthesis a final cycle of Fmoc-deprotection and acetylation using a 1:1 mixture of acetic anhydride and DMF is applied. The peptide is cleaved from the

30 MS: 3961.1

The following compounds may be prepared in a manner analogous to that of Examples 1, 24 or 25.

- EXAMPLE 26:** N<sup>ε</sup>-acetyl-[Trp<sup>10</sup>]hPTHrP(2-34)OH  
MS: 4060.4
- 5 **EXAMPLE 27:** 1-Isocaproyl-[Leu<sup>8</sup>, Trp<sup>10</sup>, Gln<sup>18</sup>, Thr<sup>33</sup>, Ala<sup>34</sup>]-  
hPTH(1-34)OH  
MS: 4091
- EXAMPLE 28:** N<sup>ε</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4097.1
- 10 **EXAMPLE 29:** N<sup>ε</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>]hPTHrP(4-34)NH<sub>2</sub>  
MS: 4009.7
- EXAMPLE 30:** N<sup>ε</sup>-2-naphthyl-sulfonyl-[Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4119.2
- 15 **EXAMPLE 31:** N<sup>ε</sup>-2-naphthoxyacetyl-[Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4111.5
- EXAMPLE 32:** N<sup>ε</sup>-2-naphthylacetyl-[Ala<sup>3</sup>, Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4080.8
- EXAMPLE 33:** N<sup>ε</sup>-benzyloxycarbonyl-[Trp<sup>2</sup>, Nal(2)<sup>10</sup>]hPTHrP(2-34)NH<sub>2</sub>  
MS: 4248.3
- 20 **EXAMPLE 34:** 3-Naphth-2-yl-propionyl-[Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4110.8
- EXAMPLE 35:** 3-Naphth-2-yl-propionyl-[Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4110.9
- 25 **EXAMPLE 36:** N<sup>ε</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>, DAla<sup>34</sup>]hPTHrP(3-34)NH<sub>2</sub>  
MS: 4095.9
- EXAMPLE 37:** N<sup>ε</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>]hPTHrP(3-31)NH<sub>2</sub>  
MS: 3788.0
- EXAMPLE 38:** N<sup>ε</sup>-3-naphth-2-yl-propionyl-[Nal(2)<sup>10</sup>]hPTHrP(7-34)NH<sub>2</sub>  
MS: 3630.0

**EXAMPLE 39:** N<sup>ε</sup>-acetyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(6-34)NH<sub>2</sub>  
MS: 3637.0

**EXAMPLE 40:** N<sup>ε</sup>-acetyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(4-34)NH<sub>2</sub>  
MS: 3903.1

5 **EXAMPLE 41:** 1-(1-amino-1-cyclopentyl-carbonyl)-  
[Leu<sup>8</sup>,Trp<sup>10</sup>,Gln<sup>18</sup>,Thr<sup>33</sup>,Ala<sup>34</sup>]hPTH(1-34)OH  
MS: 4104

Fmoc-1-aminocyclopentane-1-carboxylic acid used in the preparation of the peptide resin intermediate may be prepared, e.g. as  
10 described by G. Valle et al., 1988, in Can.J.Chem.66:2575-2582.

**EXAMPLE 42:** 1-Adamantyl-carbonyl-[Leu<sup>8</sup>,Trp<sup>10</sup>,Gln<sup>18</sup>,Thr<sup>33</sup>,  
Ala<sup>34</sup>]hPTH(1-34)OH  
MS: 4155

15 **EXAMPLE 43:** 1-(3-indolyl-carbonyl)-[Leu<sup>8</sup>,Trp<sup>10</sup>,Gln<sup>18</sup>,Thr<sup>33</sup>,  
Ala<sup>34</sup>]hPTH(1-34)OH  
MS: 4150

**EXAMPLE 44:** 1-(3-quinolyl-carbonyl)-[Leu<sup>8</sup>,Trp<sup>10</sup>,Ala<sup>16</sup>,Gln<sup>18</sup>,  
Thr<sup>33</sup>,Ala<sup>34</sup>]hPTH(1-34)OH<sup>-</sup>  
MS: 4104

20 **EXAMPLE 45:** 1-(2-naphthoyl)-[Leu<sup>8</sup>,Trp<sup>10</sup>,Gln<sup>18</sup>,Thr<sup>33</sup>,Ala<sup>34</sup>]-  
hPTH(1-34)OH  
MS: 4147

**Example 46:** N<sup>ε</sup>-(2-naphthyl)-methyl-[Trp<sup>10</sup>]hPTHrP(2-34)-OH

Methyl N-naphthoyl(2)-valinate is treated with Lawesson's  
25 reagent, S-O. Lawesson et al., Tetrahedron 37:3635 (1981) and the  
resulting methyl N-thionaphthoyl(2)-valinate is reduced using the  
procedure described for endothiopeptides by F.S. Guziec et al.,  
Tetrah. Letters 23-26 (1990). The methyl ester is hydrolyzed  
using LiOH and N-alpha-(naphthyl(2)-methyl)-valine hydrochloride  
30 obtained as a crystalline solid, mp = 205-210° (dec.). This is  
coupled using PyBOP-reagent to previously prepared, protected  
[Trp<sup>10</sup>]hPTHrP-(3-34)-O-peptide resin from which the N-alpha Fmoc-  
group has been removed. The peptide is cleaved from the resin and

purified as in Example 1.

MS: 4158.2

**EXAMPLE 47:** N<sup>ε</sup>-2-naphth-2-yl-ethyl-[Trp<sup>10</sup>]hPTHrP(2-34)OH

MS: 4171.9

5 **EXAMPLE 48:** N<sup>ε</sup>-2-naphth-2-yl-ethyl-[Ala<sup>3</sup>,Nal(2)<sup>10</sup>]hPTHrP(3-34)NH<sub>2</sub>

MS: 4066.7

**EXAMPLE 49:** N<sup>ε</sup>-succinyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-34)NH<sub>2</sub>

This peptide is prepared in a manner analogous to Example 1 but using 4-(2',4'-dimethoxyphenyl-Fmoc-amino-methyl)-phenoxy-  
10 co(polystyrene-1%-divinylbenzene), 0.63g, loading approx. 0.4 mmol/g, which may be prepared, e.g., as described in Tetrah. Letters, 28: 3787-3790 (1987) as a starting material. After coupling the last amino acid, Fmoc-His(Trt)-OH, the Fmoc-group is selectively removed as usual and the peptide resin reacted with  
15 succinic anhydride (0.5g) and DIPEA (0.86ml) in DMF. The peptide is cleaved from the resin, purified and lyophilized in the acetate form as in Example 1 to give the title compound.

MS: 3832.0

By following the procedure of Example 49, following compounds may  
20 be prepared:

**EXAMPLE 50:** N<sup>ε</sup>-succinyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-31)NH<sub>2</sub>

MS: 3522.1

**EXAMPLE 51:** N<sup>ε</sup>-succinyl-[Nal(2)<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-34)NH<sub>2</sub>

MS: 3881.7

25 **EXAMPLE 52:** N<sup>ε</sup>-glutaryl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-34)NH<sub>2</sub>

MS: 3845.6

**EXAMPLE 53:** N<sup>ε</sup>-succinyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>,DAla<sup>34</sup>]hPTHrP(5-34)NH<sub>2</sub>

MS: 3832.0

**EXAMPLE 54:** N<sup>ε</sup>-succinyl-[4-Cl-Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-34)NH<sub>2</sub>

30 MS: 3866.5

**EXAMPLE 55:** N<sup>ε</sup>-succinyl-[4-Cl-Phe<sup>5</sup>, 4-Cl-Phe<sup>6</sup>, Nal(2)<sup>10</sup>]-  
hPTHrP(5-34)NH<sub>2</sub>  
MS: 3910.2

The compounds of the invention in free form or in the form of  
5 pharmaceutically acceptable salts and complexes exhibit valuable  
pharmacological properties as indicated in animal tests and are  
therefore indicated for therapy.

The biological activity of the compounds of the invention is  
assessed in vitro by measuring their ability of stimulating  
10 (agonism) or inhibiting the PTH-stimulated (antagonism) synthesis  
of cyclic AMP in UMR 106-06 rat osteosarcoma cells according to  
the method of Marcus and Aurbach in Endocrinology, 85, 801-810  
(1969). Rat osteosarcoma UMR 106 cells are grown to confluence in  
DMEM-HAM's F12 medium (1:1) - 10% FCS in 12 well plates. The  
15 medium is then changed to medium with 2% FCS and 1-5 µCi/well  
[3H]-adenine is added. Two hours later, cells are washed twice  
with serum-free medium and incubated in DMEM - 0.1% BSA  
containing 1 mM 3-isobutyl-1-methylxanthine to exclude actions on  
phospho- diesterases. Test substances are added 20 min later  
20 either alone or together with PTH (antagonist experiment). After  
15 min, the medium is removed and the reaction is stopped and  
cAMP extracted by adding 0.5 ml ice cold 5% trichloroacetic acid.  
A carrier solution (0.5 ml/well) containing 0.2 mM of unlabelled  
adenine, adenosine, AMP, ADP, ATP, and cAMP as well as 0.4 µCi  
25 [14C]-adenosine for determination of recovery is added. [3H]-cAMP  
is separated using serial Dowex AG 50W-X4 (200-400 mesh) and  
alumina chromatography and counted according to Salomon Y. in  
Advances in Cyclic Nucleotide Research, Vol. 10, Raven Press,  
35-55, 1979. Results are calculated in % of solvent control and  
30 EC<sub>50</sub> values determined from DRC curves. Antagonist potency is  
calculated from the right ward shift of DRC curves of PTHrP or  
PTH and is given as pA<sub>2</sub> values. Compounds of the invention are  
active as antagonists at a concentration of 10<sup>-9</sup> to 10<sup>-5</sup> M. Com-  
pound of Examples 36, 37 and 49 have a pA<sub>2</sub> value in the UMR  
35 106-06 cells of 10.3; 9.7 and 9.3, respectively.

The compounds of the invention also have binding affinity to PTH  
receptors, e.g. as follows:



- Chicken [Tyr<sup>36</sup>]PTHrP(1-36)amide is iodinated to a specific activity of 2,200 Ci/mmol using the lactoperoxidase method (Anawa Lab. AG, Wangen). Monolayers of opossum kidney cells (OK1) are washed with 200 µl DMEM and HAM's F12 (1:1) containing 1% BSA and incubated at 16°C with 50,000cpm of [<sup>125</sup>I-Tyr<sup>36</sup>]chPTHrP(1-36)amide per well in the presence or absence of 1 µM [Tyr<sup>36</sup>]chPTHrP-(1-36)amide. After incubation, cells are washed with 0.5 ml medium (4°C), lysed with 0.5 ml 1N NaOH and radioactivity is determined. Specific binding is defined as total binding minus nonspecific binding. Competition curves are analyzed using SCTFIT, a non-linear regression computer program (Feyen et al, 1992, Biochem. Biophys. Res. Commun. 187:8-13) and data presented as mean pK<sub>d</sub> values (n=2 to 3). Compounds of Examples 36, 37 and 49 have a pK<sub>d</sub> value of 8.3; 7.9 and 8.4, respectively.
- Furthermore, the compounds of the invention antagonize the effect of PTH after i.v. infusion, e.g. as determined in thyroparathyroidectomized rats. 24 h after thyroparathyroidectomy, anesthetized rats are infused with PTH(1-34) and the compound to be tested via separate jugular veins. Urine is collected from the urinary bladder which is cannulated via the ventral approach. Phosphate and cAMP content in the urine and calcium and phosphate in serum are measured using standard methodology. These parameters are used to quantify antagonist potencies against PTH effects in vivo. In this test, the compounds of the invention antagonize the PTH effects when administered by i.v. infusion at a dose of from 1 µg/kg/h to 1 mg/kg/h. Compound of Example 49 completely suppresses PTH-induced phosphaturia for up to 90 min when i.v. infused at 190 µg/kg/h, PTH(1-34) being i.v. infused at 4 µg/kg/h.
- The compounds of the invention are accordingly useful for preventing or treating all conditions which are associated with increased plasma calcium caused by excessive release of PTH or PTHrP e.g. hyperparathyroidism, hypercalcemia, e.g. associated with malignancies, e.g. breast carcinomas, squamous cell carcinomas of the lung, esophagus and head and neck region and hematological malignancies, with or without bone metastases. The compounds of the invention are furthermore useful for the prevention or treatment of tumour growth, tumour penetration and ingrowth in bones stimulated by PTHrP, for treating dermatological disorders, e.g. tissue repair therapies, for

example treatment of burns, ulcerations and wounds, and for hair growth promotion.

For these indications, the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the severity of the conditions being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.1 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.1 to about 500 mg of the compounds of the invention.

The compounds of the invention may be administered in free form or in pharmaceutically acceptable salt form or complexes. Such salts and complexes may be prepared in conventional manner and exhibit the same order of activity as the free compounds. The present invention also provides a pharmaceutical composition comprising a compound of the invention in free base form or in pharmaceutically acceptable salt form or complex form in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. Unit dosage forms suitably comprise from about 0.025 to 250 mg of a compound of the invention, together with a pharmaceutical acceptable diluent or carrier therefor.

The compounds of the invention may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, or in a nasal or a suppository form. The compounds of the invention may alternatively be administered e.g. topically in the form of a cream, gel or the like for example for the treatment of the skin or hair growth as hereinbefore described.

In accordance with the foregoing the present invention further provides:

- a) a compound of the invention or a pharmaceutically acceptable salt or complex thereof for use as a pharmaceutical;
- b) a method for preventing or treating conditions and disorders as indicated above in a subject in need of such treatment, which method comprises administering to said subject an

effective amount of a compound of the invention or a pharmaceutically acceptable salt or complex thereof;

- c) a compound of the invention or a pharmaceutically acceptable salt or complex thereof for use in the preparation of a pharmaceutical composition for use in the method as in b) above.

According to a further embodiment of the invention, the compounds of the invention may be employed as adjunct or adjuvant to other therapy, e.g. in hypercalcemia to a therapy using a bone resorption inhibitor, in particular a therapy employing a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin, a biphosphonate, a diuretic or any combination thereof, or in case of tumour therapy, a cytostatic agent or any combination thereof.

In accordance with the foregoing the present invention provides in a yet further aspect:

- d) a method for preventing or treating hypercalcemia for example for preventing or treating any of the specific conditions or diseases hereinbefore set forth, in a subject in need of such a treatment which method comprises administering to said subject an effective amount of a) a compound of the invention and b) a second drug substance, said second drug substance being a therapeutic agent as indicated above.

Compounds of Examples 36, 37 and 49 are preferred for preventing or treating all conditions which are associated with increase plasma calcium caused by excessive release of PTH or PTHrP.

## SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: SANDOZ LTD.  
(B) STREET: Lichtstrasse 35,  
(C) CITY: BASLE  
(E) COUNTRY: SWITZERLAND  
(F) POSTAL CODE (ZIP): CH-4002

(A) NAME: SANDOZ PATENT GMBH  
(B) STREET: Humboldtstrasse 3  
(C) CITY: LOERRACH  
(E) COUNTRY: GERMANY  
(F) POSTAL CODE (ZIP): D-79539

(A) NAME: SANDOZ ERFINDUNGEN VERWALTUNGSGESELLSCHAFT  
M.B.H.  
(B) STREET: Brunner Strasse 59  
(C) CITY: VIENNA  
(E) COUNTRY: AUSTRIA  
(F) POSTAL CODE (ZIP): A-1230

## (ii) TITLE OF INVENTION: PEPTIDES

(iii) NUMBER OF SEQUENCES: 6

(iv) **COMPUTER READABLE FORM:**

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 38 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: unknown

## (ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Ala Val Ser Glu His Gln Leu Leu His Asn Lys Gly Lys Ser Ile Gln  
1                  5                  10                  15

Asn Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile His  
20 25 30

Thr Ala Glu Ile Arg Ala  
35

## (2) INFORMATION FOR SEQ ID NO: 2:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 34 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Ala Val Ser Glu His Gln Leu Leu His Asn Lys Gly Lys Ser Ile Gln  
1                    5                    10                    15

Asn Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile His  
                    20                    25                    30

Thr Ala

## (2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 31 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ala Val Ser Glu His Gln Leu Leu His Asn Lys Gly Lys Ser Ile Gln  
1                    5                    10                    15

Asn Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile  
                    20                    25                    30

## (2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 38 amino acids  
    (B) TYPE: amino acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ser	Val	Ser	Glu	Ile	Gln	Leu	Met	His	Asn	Leu	Gly	Lys	His	Leu	Asn
1				5					10					15	
Ser	Met	Glu	Arg	Val	Glu	Trp	Leu	Arg	Lys	Lys	Leu	Gln	Asp	Val	His
			20					25					30		
Asn	Phe	Val	Ala	Leu	Gly										
				35											

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 34 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser	Val	Ser	Glu	Ile	Gln	Leu	Met	His	Asn	Leu	Gly	Lys	His	Leu	Asn
1				5					10					15	
Ser	Met	Glu	Arg	Val	Glu	Trp	Leu	Arg	Lys	Lys	Leu	Gln	Asp	Val	His
			20					25					30		
Asn	Phe														

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 31 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

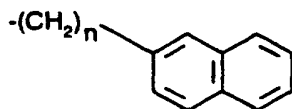
(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

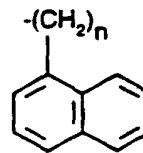
Ser	Val	Ser	Glu	Ile	Gln	Leu	Met	His	Asn	Leu	Gly	Lys	His	Leu	Asn
1				5					10					15	
Ser	Met	Glu	Arg	Val	Glu	Trp	Leu	Arg	Lys	Lys	Leu	Gln	Asp	Val	
			20					25					30		

**CLAIMS**

1. A PTH or PTHrP compound in which at least one of the amino acid residues naturally occurring in positions 2 and 10 is replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain, and optionally at least one of the amino acid residues naturally occurring in positions 3 and 6 is further replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain,
- 10 in free form or in salt or complex form.
2. A PTH or PTHrP compound in which the amino acid residue naturally occurring in position 10 is replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain, and optionally at least one of the amino acid residues naturally occurring in positions 3 and 6 is further replaced by tryptophane or another amino acid residue bearing an aromatic or heteroaromatic group on its side chain,
- 15 in free form or in salt or complex form.
- 20 3. A compound according to claim 1 wherein the amino acid residue bearing an aromatic or heteroaromatic group on its side chain is an amino acid residue wherein the side chain is optionally ring-substituted 3- or 4-pyridyl-methyl, 3-indolyl-methyl or 3-indazolyl-methyl or a radical of
- 25 formula (a), (b), (c) or (d)

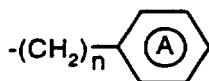


(a)

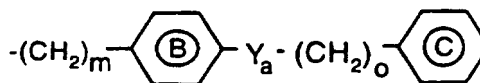


(b)





(c)



(d)

wherein

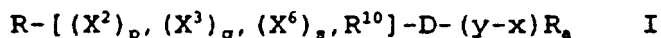
n is 1 or 2,

m is 1 or 2,

o is 0 or 1,

- 5 ring A is optionally substituted by one or more substituents selected from fluoro, chloro, nitro, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy, whereby two alkyl or two alkoxy substituents may also form together a ring structure fused to ring A, each of rings B and C independently may be substituted as
- 10 indicated above for ring A, and
- Y<sub>a</sub> is a direct bond, -CH<sub>2</sub>-, O, NH or N-C<sub>1-6</sub>alkyl.

4. A compound according to claim 1, which is a compound of formula I



15 wherein

x is a residue number selected from 31, 34, 35, 36, 37 or 38,

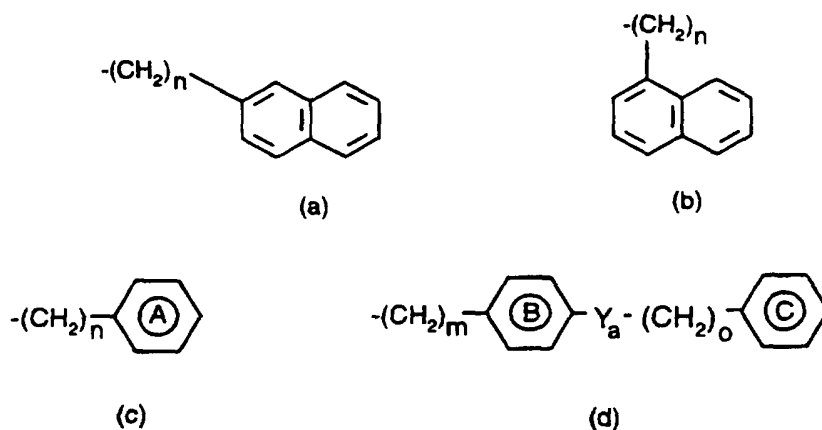
y is a residue number selected from 1, 2, 3, 4, 5, 6 or 7,

20 X<sup>2</sup> is Val or has independently one of the significances of X<sup>10</sup>,

X<sup>3</sup> is Ser or has independently one of the significances of X<sup>10</sup>,

X<sup>6</sup> is Gln or has independently one of the significances of X<sup>10</sup>,

25 R<sup>10</sup> is Asp or X<sup>10</sup>, X<sup>10</sup> being Trp or -NH-CHR'-CO- wherein R' is a radical of formula (a), (b), (c) or (d)



wherein

n is 1 or 2,

m is 1 or 2,

5 o is 0 or 1,

ring A is optionally substituted by one or more  
substituents selected from fluoro, chloro, nitro, C<sub>1-4</sub>alkyl  
and C<sub>1-4</sub>alkoxy, whereby two alkyl or two alkoxy substituents  
may also form together a ring structure fused to ring A,  
10 each of rings B and C independently may be substituted as  
indicated above for ring A, and

Y<sub>a</sub> is a direct bond, -CH<sub>2</sub>-, O, NH or N-C<sub>1-6</sub>alkyl,

D is an amino acid sequence derived either from an N-terminal  
fragment of PTHrP or PTH,

15 each of p, q and s is 1, provided that p is 0 when y > 2,

q is 0 when y > 3 and s is 0 when y > 6,

R is H, R'-CO-, R'-O-CO-, R'-O-CH<sub>2</sub>-CO-, R'-SO<sub>2</sub>-, R''',

R'''-NH-CO-, R'''-NH-CS or NH<sub>2</sub>-C<sub>1-6</sub>alkylene-CO-

20 wherein R' is C<sub>1-6</sub>alkyl; ω-carboxy-C<sub>1-6</sub>alkyl; ω-[(C<sub>1-4</sub>alkoxy)-  
carbonyl]-C<sub>1-6</sub>alkyl; C<sub>2-6</sub>alkenyl; C<sub>5-7</sub>cycloalkyl;

C<sub>5-7</sub>cycloalkyl-C<sub>1-4</sub>alkyl; or phenyl, phenyl-C<sub>1-4</sub>alkyl,

1-naphthyl, 2-naphthyl, 1-naphthyl-C<sub>1-2</sub>alkyl or  
2-naphthyl-C<sub>1-2</sub>alkyl each of which being optionally ring  
substituted by one or more substituents selected from

25 fluoro, chloro, nitro, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy; heteroaryl;  
and

R''' has independently one of the significances given for  
R' except the significances of ω-carboxy-C<sub>1-6</sub>alkyl and  
ω-[(C<sub>1-4</sub>alkoxy)-carbonyl]-C<sub>1-6</sub>alkyl; and

R<sub>a</sub> is OH or NH<sub>2</sub>,

with the proviso that at least one of X<sup>2</sup> and R<sup>10</sup> has the significance of X<sup>10</sup>.

- 5 5. A compound according to claim 1 or 4 which is derived from the N-terminal fragment of hPTH or hPTHrP.
6. A compound according to claim 1 which is selected from  
N<sup>6</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>,Dala<sup>34</sup>]hPTHrP(3-34)NH<sub>2</sub>  
N<sup>6</sup>-2-naphthyl-acetyl-[Nal(2)<sup>10</sup>]hPTHrP(3-31)NH<sub>2</sub>  
N<sup>6</sup>-succinyl-[Phe<sup>6</sup>,Nal(2)<sup>10</sup>]hPTHrP(5-34)NH<sub>2</sub>
- 10 7. A process for the production of a compound according to claim 1, in free form or in salt or complex form, which process comprises
- 15 a) removing at least one protecting group which is present in a PTHrP or PTH compound of the invention, e.g. a compound of formula I, in protected form; or
- 20 b) linking together by an amide bond two peptide fragments in protected, partially protected or unprotected form, the peptide fragments being such that the amino acid sequence of the desired PTHrP or PTH compound, e.g. of formula I, is obtained, and then effecting optionally stage a) of the process, or
- 25 c) adding a protecting group or substituent in a selective manner to the amino group of the N-terminal residue of the desired sequence or N-terminal fragment thereof in protected or unprotected form and then optionally carrying out step a),
- and recovering the PTHrP or PTH compounds thus obtained in free form, in salt form or in complex form.
- 30 8. A compound according to claim 1 in free form or in physiologically acceptable salt form for use as a pharmaceutical.
9. A pharmaceutical composition comprising a compound according to claim 1, in free form or in physiologically acceptable salt form, together with a pharmaceutically acceptable

diluent or carrier therefor.

10. A compound according to claim 1 in free form or in physiologically acceptable salt form for use as a pharmaceutical, in association with a further therapeutic agent selected from a bone resorption inhibitor and a cytostatic agent.  
5
11. A method for preventing or treating conditions which are associated with increased plasma calcium caused by excessive release of PTH or PTHrP, for preventing or treating tumor growth stimulated by PTHrP, for treating dermatological disorders and for hair growth promotion, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound according to claim 1 in free form or in a physiologically acceptable salt form.  
10  
15

## INTERNATIONAL SEARCH REPORT

Inter. application No.

PCT/EP 95/02993

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07K14/635 A61K38/29

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 269 176 (SANDOZ LTD) 2 February 1994 see page 1 - page 30; examples 82,302; claims 1,2,5,6,8-10,14,16-22,24-27,44-46 ---	1-5,7-10
A	WO,A,92 00753 (UNIV CALIFORNIA) 23 January 1992 see the whole document ---	1-11
A	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 3, 25 January 1991 MD US, pages 1997-2004, F.E.COHEN ET AL 'Analogues of PTH modified at positions 3 and 6' see the whole document --- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

10 November 1995

Date of mailing of the international search report

01.12.95

Name and mailing address of the ISA

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Authorized officer

Groenendijk, M

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 95/02993

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 451 867 (MITSUBISHI CHEM IND) 16 October 1991 see the whole document -----	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

page 2 of 2

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/02993

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 11 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Inter nal Application No

PCT/EP 95/02993

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		CA-A- 2100423	16-01-94
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